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EXAMINER	
LIU, SUE XU	
ART UNIT	PAPER NUMBER
1639	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,684	WALDMAN, SCOTT A.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,25-27,30-34,36,39,40,42-48,50-56 and 62-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/18/09;5/1/09;4/28/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 1-22, 24, 28, 29, 35, 37, 38, 41, 49 and 57-61 have been cancelled.

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 are currently pending.

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 are being examined in this application.

Election/Restrictions

2. Applicant's election without traverse of Group I (claims 23-44 and 67), and species election of peptide having amino acid sequence of SEQ ID NO: 2 as the ST receptor binding ligand, and 5-fluorouracil as the species of active agent, in the reply entered, 02/01/05, is as previously acknowledged.

Priority

3. This application is a continuation of 09/263,477 (now abandoned), filed 3/5/99, which is a continuation of 08/583,447 (now US Patent 5,879,656), filed 1/5/96, which is a continuation-in-part of 08/141,892 (now US Patent 5,518,888), filed 10/26/93.

4. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 08/141,892, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The Grandparent patent application 08/141,892 (Now US Patent 5,518,888) does not appear to provide supports for the claimed invention regarding SEQ ID NO: 55 and 56, which are recited in Claims 25, 32, 43, 45, and 50 of the instant application.

Thus, the instant claims 25, 32, 43, 45, and 50 which recite sequences not disclosed in the parent applications are entitled only to the filing date of the application 08/583,447.

The filing date of the instant claimed invention of recited in Claims 25, 32, 43, 45, and 50 (in particular, SEQ ID Nos 55 and 56) is determined as the filing date of the US Application 08/583,447, **01/05/1996**.

Information Disclosure Statement

5. The IDS filed on 12/18/09, 5/1/09 and 4/28/09 have been considered. See the attached PTO 1449 forms.

Specification

6. Applicant's amendments to the instant specification including the Abstract filed on 10/9/09 is acknowledged and entered.

Claim Objection(s) / Rejection(s) Withdrawn

7. All previous claim Objection(s) / Rejection(s) as set forth in the previous Office action (mailed 4/9/09) that are not repeated and/or maintained in the instant Office action are withdrawn.

New / Maintained Claim Objection(s) / Rejection(s)

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Trouet, Houghten, Hussain, and Gluck

Claims 23, 25-27, 30, 32-34, 42-43, 45-48, 50-56 and 62-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Trouet** et al (PNAS. Vol. 79: 626-629; 1982), in view of **Houghten** (WO 84/02700; 7/19/1984), **Hussain** et al (EP 0341661; 11/15/1989), and **Gluck** et al (US

6,040,167; 3/21/2000; priority date 11/2/1992 or earlier; cited previously), and if necessary in view of **Guzman-Verduzco** et al. (Molecular Microbiology. Vol.4(2): 253-64; 1990). This rejection is necessitated by applicant's amendments to the claims.

The instant claim **23** recites a pharmaceutical composition that can be used to treat metastatic colorectal cancer comprising;

a) a ST receptor binding ligand selected from the group consisting of: antibodies that bind to ST receptor, antibody fragments that bind to ST receptor and peptides that bind to ST receptor;

b) a non-peptide radiostable cytotoxic or cytostatic agent; and,

c) a pharmaceutical carrier or diluent."

The instant claim **42** recites a similar composition except in part b): "a radiostable active agent, wherein the radiostable active agent is a cytotoxic or cytostatic agent" as well as other components including liposome.

The instant claim **48** recites a similar composition except in part b): "an active agent selected from the group consisting of: cytotoxic or cytostatic agent" as well as other limitatuions including unconjugated.

Trouet et al, throughout the publication, teach conjugating drugs such as "duanorubicin" with various proteins, peptides or polypeptides as therapeutic reagents (e.g. Abstract), which the drugs such as "duanorubicin" read the non-peptide radiostable cytotoxic or cytostatic agent of **clms 23**, **30**, **42**, **46**, **48**, **53-56**, **etc** (e.g. **part b** of claim 23). The reference also teaches various buffers and/or pharmaceutical reagents (such as water, buffers, etc) were added to the drug (e.g. p.627), which reads on the pharmaceutical carrier of **clms 23**, **30**, **42**, **46**, **48**, **53-56**, **etc** (e.g. **part c** of claim 23). The reference also teaches the need to associate peptides (or proteins) with therapeutic agents (or drugs) for carrying various drugs (e.g. p.626). The reference also teaches using peptides (or proteins) as carriers for selective targeting of anti-tumor drugs (such as methotrexate). (e.g. p.626, para 1).

Trouet et al., do not explicitly teach a pharmaceutical composition comprising a "a ST receptor binding ligand" as recited in **clms 23**, **47**, **53**, **etc**. The Trouet reference also does not explicitly teach the pharmaceutical composition comprises a liposome as recited in **clm 42**.

However, **Houghten** et al, throughout the patent, teach vaccine compositions (read on pharmaceutical composition) comprising ST receptor binding moiety (i.e. bacteria enteriotoxin polypeptides/peptides) (e.g. Abstract), which reads on the ST receptor binding peptides of **clms 23**, **42**, and **48**. The ST receptor binding peptides of the reference read on the ST receptor binding ligand of **clm 23**. The reference also teaches the composition can have monomer or multimers of the toxins (e.g. pp.8+; 10+), or conjugating the ST toxin to other toxins or to immunoglobulin G (e.g. p.16, lines 10+; p.17, lines 10+), which the additional toxin peptides read on the "radiostable active agent" that is a therapeutic agent of **clms 42**, **48**, **54**, and **55** because the instant specification defines the term "radiostable" as compounds which are not radioactive at p. 7, para 4. In addition, the instant specification broadly defines the term "therapeutic agent" as "chemotherapeutics, toxins, radiotherapeutics, targeting agents or radiosensitizing agents" at p.7, lines 15+; the instant specification broadly defines the term "imaging agent" as "compounds which can be detected" at p.8, lines 12+. Thus, at least the additional toxin peptides of the reference read on the "toxins" encompassed by the term "therapeutic agent" or the "imaging agent" (see Houghten, p.10, lines 9+ and p.15 for diagnostic and vaccine uses) as defined by the instant specification. The reference also teaches using enterotoxin as carrier peptides for delivering other agents (e.g. p.3; pp.38+) in general, as well as administering multimer of ST toxin (e.g. p.26+).

The reference also teaches buffers in which the said multimers are contained for various uses such as aqueous composition comprising various buffers (e.g. pp. 13-14) or various physiologically acceptable diluents (e.g. p.23, lines 28+), which reads on the pharmaceutical carrier or diluent of **clms 23**, **42** and **48**. The "buffers" of the reference are not "conjugated" to either the peptides or the active agent, and thus read on the limitation of "said composition is unconjugated" of **clm 48** as the recitation is reasonably and broadly interpreted. The reference discloses ST receptor binding peptides comprising various amino acid sequences such as the ones listed on pg 51 (Formula VI) and pg 53, which read on the SEQ ID No 3 of the instant **clms 25-27**, **32-34**, **38**, **43**, **45**, **50-52** and **62-66**. The recitation "wherein said fragments and derivatives bind to ST receptor" of the instant claims (e.g. Claim 25) is an inherent property of the claimed peptides or ligands. As discussed above, the amino acid sequence of the reference is the same as the instant claimed "ST receptor" binding peptides, and the peptides/polypeptides of the reference also possess the needed disulfide bonds for receptor binding. Thus, the peptides of the reference are structurally the same as the instant claimed peptides and possess the same function/inherent property. In addition, the instant claim recites "peptides **having an** amino acid sequence SEQ ID NO:2…" which recitation does not dictate that the instant peptides consist of only the amino acid sequence of the claimed SEQ ID NOs. The said claim language is open ended, and thus the sequence of the reference reads on the instant claimed peptides.

The Houghten reference also teaches formulating the composition into an injectable composition for administering to mice or rabbits through injection. (e.g. p.132), which read on the injectable pharmaceutical composition of **clms 41**, **57** and **58**.

The peptide of the reference (as discussed above) inherently possess the property of binding to ST receptor activated guanylyl cyclase C as recited in **clms 23, 42** and **67**, as evidenced by the instant specification (spec. p.13, lines 30+). As the peptide of the reference is structurally the same as the peptide of the instant claims (which the instant specification discloses to possess the property of activating guanylyl cyclase C), the peptide of the reference would have the same property and/or function of activating the same target.

The reference also teaches using the peptide in an injectable formula (e.g. p.132), which reads on the "injectable pharmaceutical composition" of **clm 42**.

In addition, **Hussain** et al, throughout the publication, teach conjugating non-peptide compounds such as aminoboronic acid derivatives to peptides as pharmaceutical compositions. (e.g. pp. 2-3). The reference also teaches the advantages of including a chemical compound to peptides as pharmaceutical composition such as to "stabilize and improve the delivery of pharmacological active peptides" (e.g. p.3, para 1).

Further, **Guzman-Verduzco** et al, throughout the publication, teach using heat-stable enterotoxin (i.e. ST receptor binding peptides) as "carriers" for delivering other molecules. (e.g. Abstract). The reference teaches the ST toxin peptide can be used as a carrier for cellular delivery (e.g. pp.253+).

Finally, **Gluck** et al, throughout the patent, teach a similar pharmaceutical composition comprising a liposome vesicle (part (a) of Claim 1 of the reference), a fusion peptide (part (b) of Claim 1), and a protein for binding receptor (part (d) of Claim 1). The reference teaches the benefits or advantages of using liposome vesicles to deliver particular drugs (col. 1, lines 55+).

The advantages include facilitating transporting the drug through normally impermeable barriers, and improving drug selectivity and reduction in toxicity, etc. (col. 1, lines 57+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to make a composition comprising a ST receptor binding ligand (i.e. peptides or proteins) and a non-peptide therapeutic agent as well as using liposome vesicles to deliver various drugs of interest.

A person of ordinary skill in the art would have been motivated at the time of the invention to make a pharmaceutical composition comprising a carrier peptide such as a ST receptor ligand and a therapeutic agent such as duanorubicin or aminoboroni acid, because both Hussain et al and Trouet et al, and if necessary, Guzman et al teach using peptides or proteins as carrier for drug delivery are routine and known in the art, and both of the references teach the need to use carrier peptides for drug delivery such as increased target selectivity and increased drug stability as discussed above. In addition, all the references teach pharmaceutical compositions comprising a carrier peptide (or protein) with an active or therapeutic agent for effective drug delivery, it would have been obvious to one skilled in the art to substitute one agent or one peptide for the other to achieve the predictable result of making a pharmaceutical composition. See *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396.*

A person of ordinary skill in the art would have been motivated at the time of the invention to use liposome as part of a pharmaceutical composition that comprise fusion peptides (or conjugates) with active drug agents, because using liposome vesicle to deliver drugs offer many advantages such as high permeability and low toxicity as discussed supra.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Houghten, Hussain and Trouet (and/or Guzman) references have all demonstrated success generation of compositions comprising both peptides and other agents such as non-peptide agents. A person of ordinary skill in the art would also have reasonable expectation of success of achieving such modifications because Gluck et al have demonstrated the utilization of liposome vesicle as part of a pharmaceutical composition that comprise peptides, and receptor binding proteins.

Discussion and Answer to Argument

9. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traversed the above rejection by arguing each individual reference does not teach all elements of the claimed invention. (Reply, pp.24).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants assert Houghten "neither teaches nor suggests combining the disclosed peptide with a cytotoxic or cytostatic agent" and the inclusion of cytotoxic/cytostatic agent would "have been contrary to the purpose of generating an immune response". (Reply, p.24).

Applicants are respectfully directed to the above new claim rejection, where Houghten is not used as the primary reference (i.e. the reference being modified). See MPEP 2143.01 II. As discussed supra, the Trouet reference teaches a therapeutic drug in combination with peptide carriers. The above rejection is modifying the Trouet's teaching by substituting the peptide carrier of Trouet with the peptide carrier of Houghten (the ST toxin peptide), which modification would not defeat the purpose of the Trouet reference.

Further, contrary to applicant's assertion, combining the ST peptide (i.e. the heat stable enterotoxin) with cytotoxic/cytostatic agent would also not be contrary to the purpose of the Houghten reference. The ST peptide of the Houghten reference is in itself a toxin/cytotoxin/enterotoxin (as disclosed by the Houghten reference as well as the instant specification). It is not clear how adding another cytotoxin to the ST toxin would defeat the purpose of the Houghten reference. Additionally, the ST toxin is used for various purposes. The use of the ST peptides a vaccine composition is only one embodiment of the reference's teachings.

Applicants also the Hussain reference "teaches away from the claimed invention." (Reply, pp.24-25).

Applicants reasoned that because the Hussain reference teaches "absorption based, non-injection routes of administration," the Hussain reference "teaches away" from the modification. This is not persuasive. The Hussain reference was cited to provide reasons for one skill in the art to include peptide carrier with drug compounds. Contrary to applicant's assertion, the Hussain reference does teach injectable formulation (e.g. p.3, lines 20+).

"Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971)." (see MPEP 2123).

Further, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004)." (see MPEP 2141.02).

In the instant case, applicants have not pointed to the specific teachings of the Hussain reference to show that the said reference actual "criticize, discredit or otherwise discourage" combining the cytotoxic drug of the Trouet reference with the ST peptide of the Houghten reference.

Houghten and Others

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Trouet** et al (PNAS. Vol. 79: 626-629; 1982), in view of **Houghten** (WO 84/02700; 7/19/1984), **Hussain** et al (EP 0341661; 11/15/1989), and **Gluck** et al (US 6,040,167; 3/21/2000; priority date 11/2/1992 or earlier; cited previously) and if necessary in view of **Guzman-Verduzco** et al. (Molecular Microbiology. Vol.4(2): 253-64; 1990), as applied to claims 23, 25-27, 30, 32-34, 42-43, 45-48, 50-56 and 62-67 above, and further in view of **Lee** et al (US 5,183,805; 2/2/1993; cited previously). This rejection is necessitated by applicant's amendments to the claims.

Trouet et al, throughout the publication, teach conjugating drugs such as "duanorubicin" with various proteins, peptides or polypeptides as therapeutic reagents as discussed supra.

Houghten et al, throughout the patent, teach pharmaceutical compositions comprising conjugates of ST receptor binding moiety and another agent as discussed supra.

Hussain et al, throughout the publication, teach conjugating non-peptide compounds such as aminoboronic acid derivatives to peptides as pharmaceutical compositions as discussed supra.

Guzman-Verduzco et al, throughout the publication, teach using heat-stable enterotoxin as a carrier, as discussed supra.

Gluck et al, throughout the patent, teach a similar pharmaceutical composition comprising a liposome vesicle, as discussed supra.

The combination of the Houghten, Hussain, Trouet and Gluck teachings as discussed supra is hereby incorporated by reference in its entirety.

The combination of the Houghten, Hussain, Trouet and Gluck (and/or Guzman-Verduzco) references does not explicitly teach a pharmaceutical composition comprising 5-fluorouracil as recited in **claims 31**, **36**, **39**, **40** and **44**.

However, **Lee** et al, throughout the patent, teach compositions comprising peptides and other compounds for cancer therapeutic applications (see Abstract). The reference particularly teaches conjugating peptides (such as EGF peptides) with chemotherapeutic agents including 5-fluorouracil (e.g. col.15, lines 20+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to make a composition comprising a ST receptor binding ligand (i.e. peptides or proteins) and a chemotherapeutic drug such as 5-fluorouracil.

A person of ordinary skill in the art would have been motivated at the time of the invention to make a pharmaceutical composition comprising a carrier peptide such as a ST receptor ligand and a therapeutic agent such as 5-fluorouracil, because Lee et al teach the advantages of combining different drugs for synergistic effects such as enhanced drug delivery to specific tumor cells (e.g. col.15, lines 20+). In addition, all the above cited references teach pharmaceutical compositions comprising a carrier peptide (or protein) with an active or therapeutic agent for effective drug delivery, it would have been obvious to one skilled in the art to substitute one agent or one peptide for the other to achieve the predictable result of making a pharmaceutical composition for effective drug delivery. See *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396*.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Houghten, Hussain, Trouet, Gluck and Lee references have all demonstrated success generation of compositions comprising both peptides and other agents such as non-peptide agents.

Discussion and Answer to Argument

10. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below:

Applicants traversed the above rejection with the same argument as the traversal over the first appearing rejection under 103(a) of the instant office action. Thus, applicants are respectfully directed to the discussion supra for answer to arguments.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5,962,220

12. Claims 23, 25-28, 33, 34, 38, 40-42, 45, and 47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, and 6 of U.S. Patent No. 5,962,220 (cited in the previous Office action 5/3/05), and in view of **Gluck** et al (US 6,040,167; 3/21/2000; priority date 11/2/1992 or earlier) and **Trouet** et al (PNAS. Vol. 79:

626-629; 1982), or alternatively, in view of Gluck and **Lee** et al (US 5,183,805; 2/2/1993; cited previously). This rejection is necessitated by applicant's amendments to the claims.

The '220 patent claims a pharmaceutical composition comprising a pharmaceutical carrier or diluent, and a conjugate compound comprising a ST receptor binding moiety and an active moiety (Claims 5 and 1 of the '220 patent), which reads on the receptor binding ligands of **clm 23**. The '220 patent also claims "active moiety" is an antisense molecule (claim 3), which reads on the non-peptide active (or therapeutic) agent of the instant claims (e.g. **clm 23**). The '220 patent also claims specific SEQ ID Nos 2, 3, and 5-54, which are the same as the SEQ ID Nos in the instant **clms 25-28, 33, 34, 38, and 40**.

The '220 patent does not explicitly claim the agent is a cytotoxic or cytostatic agent as recited in claim 23 or other claims. The '220 patent also does not specifically claims the pharmaceutical composition comprises a liposome.

However, Gluck et al, throughout the patent, teach a similar pharmaceutical composition comprising a liposome vesicle (part (a) of Claim 1 of the reference), a fusion peptide (part (b) of Claim 1), and a protein for binding receptor (part (d) of Claim 1). The reference teaches the benefits or advantages of using liposome vesicles to deliver particular drugs (col. 1, lines 55+). The advantages include facilitating transporting the drug through normally impermeable barriers, and improving drug selectivity and reduction in toxicity, etc. (col. 1, lines 57+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to using liposome vesicles to deliver various drugs.

A person of ordinary skill in the art would have been motivated at the time of the invention to use liposome as part of a pharmaceutical composition that comprise fusion peptides

(or conjugates) with active drug agents, because using liposome vesicle to deliver drugs offer many advantages such as high permeability and low toxicity as discussed supra.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications because Gluck et al have demonstrated the utilization of liposome vesicle as part of a pharmaceutical composition that comprise peptides, and receptor binding proteins.

Additionally, **Trouet** et al, throughout the publication, teach conjugating drugs such as "duanorubicin" with various proteins, peptides or polypeptides as therapeutic reagents (e.g. Abstract), which the drugs such as "duanorubicin" read on the non-peptide radiostable cytotoxic or cytostatic agent.

Or, **Lee** et al, throughout the patent, teach compositions comprising peptides and other compounds for cancer therapeutic applications (see Abstract). The reference particularly teaches conjugating peptides (such as EGF peptides) with chemotherapeutic agents including 5-fluorouracil (e.g. col.15, lines 20+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to make a composition comprising a ST receptor binding ligand (i.e. peptides or proteins) and a non-peptide therapeutic agent such as duanorubicin or 5-fluorouracil.

As the cited references teach pharmaceutical compositions comprising a carrier peptide (or protein) with an active or therapeutic agent for effective drug delivery, it would have been obvious to one skilled in the art to substitute one agent or one peptide for the other to achieve the

predictable result of making a pharmaceutical composition. See *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396*.

6,087,109

13. Claims 23, 25-28, 33, 34, 38, and 40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 and 13 of U.S. Patent No. 6,087,109 (Claims 5 and 1 of the '220 patent), and in view of **Trouet** et al (PNAS. Vol. 79: 626-629; 1982) or **Lee** et al (US 5,183,805; 2/2/1993; cited previously). This rejection is necessitated by applicant's amendments to the claims.

The '109 patent claims a pharmaceutical composition comprising a pharmaceutical carrier or diluent, and a conjugate compound comprising a ST receptor binding moiety and an active moiety (Claims 7 and 1 of the '109 patent), which reads on the receptor binding ligands of **clm 23**. The '109 patent also claims "active moiety" is an antisense molecule (claim 3), which reads on the non-peptide active (or therapeutic) agent of the instant claims (e.g. **clm 23**). The '109 patent also claims specific SEQ ID Nos 2, 3, and 5-54, which are the same as the SEQ ID Nos in the instant **clms 25-28, 33, 34, 38, and 40**.

The '109 patent does not explicitly claim the agent is a cytotoxic or cytostatic agent as recited in claim 23 or other claims.

However, **Trouet** et al, throughout the publication, teach conjugating drugs such as "duanorubicin" with various proteins, peptides or polypeptides as therapeutic reagents (e.g. Abstract), which the drugs such as "duanorubicin" read on the non-peptide radiostable cytotoxic or cytostatic agent.

Or, **Lee** et al, throughout the patent, teach compositions comprising peptides and other compounds for cancer therapeutic applications (see Abstract). The reference particularly teaches conjugating peptides (such as EGF peptides) with chemotherapeutic agents including 5-fluorouracil (e.g. col.15, lines 20+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to make a composition comprising a ST receptor binding ligand (i.e. peptides or proteins) and a non-peptide therapeutic agent such as duanorubicin or 5-fluorouracil.

As the cited references teach pharmaceutical compositions comprising a carrier peptide (or protein) with an active or therapeutic agent for effective drug delivery, it would have been obvious to one skilled in the art to substitute one agent or one peptide for the other to achieve the predictable result of making a pharmaceutical composition. See *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396.*

7,097,839

14. Claims 23 and 28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24, 26, 28, 29 and 33-41 of U.S. Patent No. 7,097,839, and in view of **Trouet** et al (PNAS. Vol. 79: 626-629; 1982) or **Lee** et al (US 5,183,805; 2/2/1993; cited previously). This rejection is necessitated by applicant's amendments to the claims.

The '839 patent claims methods using a pharmaceutical composition comprising peptides as ST receptor binding moiety, the reference active moiety is a therapeutic agent, and

pharmaceutical acceptable carrier or diluent (e.g. Claims 11 and 20), which reads on the pharmaceutical composition of the instant **clms 23 and 28**. The '839 patent also claims the active agents are methotrexate, doxorubicin, 5-fluorouracil, etc. (e.g. Claim 22), which reads on the same active agents as the instant **clms 30, 31, 36, and 39.** The '839 patent also claims the pharmaceutical composition is in an injectable formulation (e.g. Claim 6), which reads on the injectable formulation of **clm 41**.

The '839 patent does not explicitly claim the agent is a cytotoxic or cytostatic agent as recited in claim 23 or other claims.

However, **Trouet** et al, throughout the publication, teach conjugating drugs such as "duanorubicin" with various proteins, peptides or polypeptides as therapeutic reagents (e.g. Abstract), which the drugs such as "duanorubicin" read on the non-peptide radiostable cytotoxic or cytostatic agent.

Or, **Lee** et al, throughout the patent, teach compositions comprising peptides and other compounds for cancer therapeutic applications (see Abstract). The reference particularly teaches conjugating peptides (such as EGF peptides) with chemotherapeutic agents including 5-fluorouracil (e.g. col.15, lines 20+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to make a composition comprising a ST receptor binding ligand (i.e. peptides or proteins) and a non-peptide therapeutic agent such as duanorubicin or 5-fluorouracil.

As the cited references teach pharmaceutical compositions comprising a carrier peptide (or protein) with an active or therapeutic agent for effective drug delivery, it would have been

obvious to one skilled in the art to substitute one agent or one peptide for the other to achieve the predictable result of making a pharmaceutical composition. See *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396*.

'901

15. Claims 23, 25-27, 48, 50, 51, 52, 54 and 55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10, 12 and 15-17 and 20-22 of copending Application No. 11/494,901 (US 20060269477). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed invention in the '901 application reads on the instant claimed invention.

The '901 application claims a pharmaceutical composition comprising "a pharmaceutical acceptable carrier…", "a ST receptor binding moiety," and "an active moiety", wherein the active moiety is a therapeutic agent or a cytotoxic agent as recited in claims 10 and 12 of the '901 application. The '901 application also recites the same SEQ ID Nos as the ones listed in the instant claims. Because the pharmaceutical carrier is "unconjugated" from the compounds, the claimed invention as recited in claims 10 and 12 of the '901 application read on the composition of the instant claim 48. The '901 application also claims methods of treating using a pharmaceutical composition comprising "a carrier", "a ST receptor ligand", and "a nucleic acid molecule" as recited in claim 22, which composition reads on the instant claimed invention as recited in claim 23.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Discussion and Answer to Argument

16. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants state applicant will file appropriate terminal disclaimers upon indication that the pending claims would be otherwise allowable for the following patents:

5,962,220; 6,087,109; 7,097,839. (Reply, p.15+)

However, the instant claims have not been indicated as allowable, and applicants have not filed the appropriate terminal disclaims to overcome the above rejections. Thus, the said rejections are maintained for the reasons of record.

Applicants also state the provisional double patenting rejection requires no action at this time. (Reply, p.15-16).

However, the instant claims are not otherwise allowable, thus the said claim rejection is maintained for the reasons of record.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/
Primary Examiner, Art Unit 1639
1/25/10